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REVIEW

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Composition and diversity of the pulmonary microbiome in acute respiratory distress syndrome: a systematic review

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Abstract

The pulmonary microbiome plays a crucial role in respiratory health and disease, with growing evidence suggesting its involvement in the pathophysiology of acute respiratory distress syndrome (ARDS). This systematic review synthesises current findings on primarily the composition of the lung microbiome in ARDS patients, and secondarily evaluates the microbial diversity, bacterial abundance and their potential clinical implications on disease severity, ventilator-free days and mortality. A comprehensive literature search identified 11 studies, including 660 patients, 466 of whom had ARDS, examining lung microbial alterations in ARDS using different sequencing technologies. While studies reported different, but consistent changes in microbial compositions, findings on diversity varied across studies. Trends suggest an increased prevalence of specific opportunistic pathogens, particularly members of the gut-associated *Enterobacteriaceae* family, which was also shown to be associated with fewer ventilator-free days and mortality, although differences in patient populations, study methodologies, and sequencing techniques influenced the results. The relationship between the pulmonary microbiome and clinical outcomes, remains an area of active investigation. *Clinical trial Registration*:the PROSPERO ID CRD42023467660.

Keywords Acute lung failure, Mechanical ventilation, Microbiota, Sepsis

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Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening clinical syndrome characterised by severe impairment of gas exchange leading to acute hypoxaemic failure [1]. The treatment of ARDS remains challenging, despite various interventions, including the use of lung protective ventilation, prone positioning, possible corticosteroid therapy for the most severe cases, and extracorporeal membrane oxygenation in refractory hypoxaemia [2].

ARDS is traditionally divided into direct pulmonary insults caused by, e.g., viral and bacterial pneumonia, aspiration of gastric contents, and lung contusion, while common extrapulmonary causes include sepsis,

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acute pancreatitis, and major trauma [3]. Regardless of aetiology, ARDS is characterised by diffuse pulmonary inflammation and injury to the alveolar epithelium and micro-vascular endothelium driven by an abundance of proinflammatory cytokines and chemokines, along with neutrophil extravasation, which further perpetuates inflammation. This, in turn, leads to increased alveolar-capillary permeability and leakage of protein-rich oedema fluid into the interstitium and alveolar airspaces [4].

The human microbiome influences immune responses, modulates inflammation, and interacts with host physiology in ways that may impact ARDS outcomes [5–7]. The lungs, once thought to be sterile, are now known to harbour a dynamic, low-biomass microbiome, even in health. Advances in sequencing technology have revealed that the microbiome is metabolically active and varies across health and disease states [8]. Hitherto, the complete composition of the pulmonary microbiome in the healthy state remains to be fully determined, but the predominant 'core' phyla include Pseudomonadota, Bacteroidota, Actinomycetota, and Bacillota, together accounting for between 63 and 97% of the total organisms identified in the lungs [9–12]. Collectively, the lung microbiome plays an inherent role in colonisation resistance by occupying ecological niches and utilising available nutrients, thereby preventing the establishment of harmful microbes [13–15].

A failure of these processes may contribute to the development and progression of ARDS. Dysbiosis is a shift or change in the normal microbial composition of the microbiome, including microbial abundance and/or diversity, which may impair the protective functions of the lung microbiome. These impairments can trigger immune dysregulation, disrupt epithelial barrier integrity, and hinder resistance to pathogen colonisation, while also exposing the lungs to microbial metabolites, such as short-chain fatty acids [15, 16]. Shifts in abundance, such as overgrowth of potential pathogenic microbes and reduced microbial diversity, have been suggested to be linked to increased inflammation and impaired recovery, such as prolonged ventilation [17, 18].

The objective of this systematic review is primarily to characterise the lung microbiome composition in ARDS, and secondly to assess lung microbiome diversity and bacterial abundance, and their potential impact on clinical outcomes in patients with ARDS.

Methods

This systematic review was reported with reference to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement [19]. The protocol is registered on the PROSPERO database (ID: CRD42023467660).

Search strategy and selection criteria

We searched PubMed, EMBASE, Cochrane Library, Web of Science, and clinicaltrials.gov databases for English articles. The search was last updated on 04.03.2025. The aim was to identify observational studies examining the lung microbiome in patients diagnosed with ARDS. The search strategy employed the following keywords (including relevant MeSH terms): ("lung"OR"pulmonary") AND"microbiome"AND ("acute respiratory distress syndrome"OR"ARDS"OR"acute lung injury"). The full search strategies can be found in the supplementals (Additional file 1). Additional studies were identified by searching the reference list of relevant reviews and included studies. No restrictions were applied regarding publication date.

The types of studies included in the review were observational cohort and case–control studies involving human participants admitted to the intensive care unit (ICU), focusing on the lung microbiome in either endotracheal aspirates (ETA) or bronchoalveolar lavage (BAL) fluid. The participants in the studies had to be adults aged > 18 years and diagnosed with ARDS according to the Berlin definition [20]. Studies were excluded if they were not based on humans, did not involve patients diagnosed with ARDS specifically, or represented patients diagnosed with ARDS caused by coronavirus disease or burns. Studies were also excluded if microbiome data were not based on sequencing methods.

According to screening and data extraction, two authors (KS and JU) independently screened titles and abstracts, followed by full-text assessment to identify eligible reports. Data were extracted separately by the two authors in a standardised form. Any disagreements during screening and data extraction between the two authors were discussed to reach an agreement.

Data synthesis and outcomes

We extracted the name of the first author, publication year, sample size, inclusion/exclusion criteria, essential research methods, sources used for recruiting control subjects, and central patient demographics, including the cause of ARDS. Studies were defined as *pulmonary* ARDS (pARDS) if patients had ARDS due to a direct insult, *extrapulmonary* ARDS (epARDS) if patients had an indirect insult, or *mixed-type* ARDS (mtARDS) if studies included both direct and indirect causes.

The primary outcome was differences in microbiota composition extracted at the species, genus, phylum, or family level. In relation to the microbiota composition, principal components analysis (PCA) or principal coordinates analysis (PCoA) was noted to visually assess the community composition. Additionally, information was extracted on various microbiome parameters, such as the microbial diversity, including α-diversity, which

quantifies microbial species diversity within a single sample or community using metrics like the Shannon diversity index, Simpson's index, or species richness (Chao1 index), and β-diversity, which assesses differences in microbial composition between samples [21]. Secondary outcomes included the relative abundance—referring to the proportion of specific microbes in a sample—and clinical outcomes such as disease severity, ventilator-free days and mortality.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the selected articles [22]. The NOS comprises three domains, with a maximum of nine stars achievable: selection (including the definition and representativeness of cases, selection of controls, and definition of controls), comparability (assessing baseline characteristics comparability), and exposure (evaluating exposure ascertainment, method consistency between cases and controls, and attrition rate). Based on the evaluation results within each domain, a total score was calculated for each study and then converted to Agency for Healthcare Research and Quality (AHRQ) standards, categorising them as either good, fair, or poor. Thresholds for converting the NOS can be found in the supplementals (Additional file 2).

Results

Study selection

A total of 748 studies were identified from the search strategy, and of those, 167 were excluded after removing duplicates. After carefully reviewing the titles and abstracts, an additional 492 were excluded based on their lack of relevance to the specific research question or their focus on the lung microbiome in other lung diseases. Following a full-text assessment of the remaining 89 articles, 78 were excluded due to study design, study population, or insufficient or unavailable data on the lung microbiome, including missing subgroup analysis of ARDS-specific patients. The remaining 11 studies were included in the present study (for PRISMA flow diagram, see Fig. 1), divided into six cohorts and five case–control studies, with sample sizes ranging from 13 to 156 patients, encompassing a total of 660 patients, of which 466 were diagnosed with ARDS.

Study characteristics

The study characteristics are outlined in Table 1. Briefly, four studies included mtARDS [23–26], four focused on pARDS [27–30], and four on epARDS [27, 31–33].

Mixed-type ARDS. In the studies examining mtARDS, comparator groups included critically ill and mechanically ventilated patients without ARDS (nonARDS) in Dickson et al. 2020 and Kyo et al. [24, 25], healthy volunteers in Dickson et al. 2016 [23], and no comparator in Ye et al. [26].

Pulmonary ARDS. Studies on pARDS included patient populations with bacterial and viral pneumonia [27–30]. Zhang et al. compared pARDS to epARDS due to sepsis and included controls with mild pulmonary infections [27], whereas Hernández-Terán et al. and Du et al. had no control groups [28, 29]. Imbert et al. compared a group of patients with ARDS due to influenza, bacterial community-acquired pneumonia (CAP), or COVID-19 [30].

Extrapulmonary ARDS. Schmitt et al. investigated ARDS caused by abdominal sepsis, compared to patients undergoing elective oesophageal resection [31], and Panzer et al. followed severe trauma patients to assess epARDS development over 48 h [32]. Lastly, Li et al. and Zhang et al. examined epARDS caused by sepsis, with extrapulmonary focus of infection [27, 33]. Based on disease and intestinal markers, Li et al. further divided patients into enteric and non-enteric ARDS.

In several of the included studies, the broader study population consisted of critically ill patients admitted to the ICU, among whom a subgroup developed ARDS. The diagnostic information for the nonARDS comparators was scarce, but we identified diagnoses such as pneumonia, influenza, COVID-19, severe blunt trauma, or other critical illnesses (see Table 1).

ETA-based studies. All studies included BAL or mini-BAL as their primary sampling method, except for Panzer et al. and Imbert et al. that analysed ETA only [30, 32]. Studies using ETA as the sole sampling method are described separately throughout the manuscript due to potential concerns about their ability to represent the lower airway microbiome accurately.

Sequencing methods. All studies used amplicon sequencing, targeting the 16S rRNA or metagenomic shotgun sequencing. Further details are presented in Table 2.

Quality of studies

Of the eleven included studies, four were rated as good quality [24, 28, 30, 32], two as fair [25, 27], and five as poor quality [23, 26, 29, 31, 33] based on standardised criteria for cohort and case–control designs (see Additional file 2). Limitations in poor-quality studies are primarily related to unclear selection of controls, lack of adjustment for key confounders (e.g. antibiotics or infection type), and absence of pre-exposure microbiome data in cohort designs. All studies exhibited no apparent limitations in terms of outcome assessment [22].

Due to marked heterogeneity within and across studies, it was not feasible to conduct pooled estimates or meta-analyses of the investigated variables.

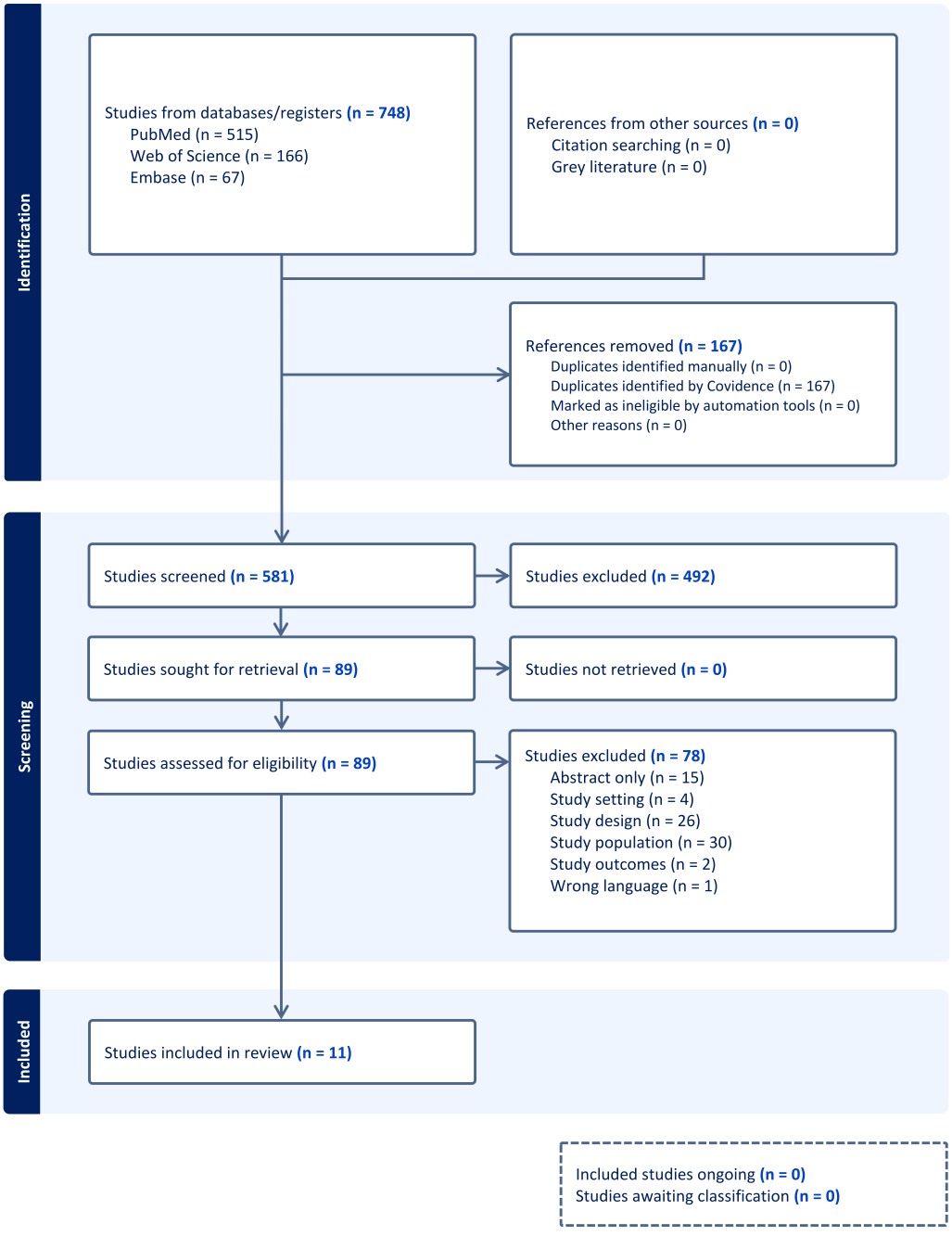
Identification
Studies from databases/registers (n = 748)
PubMed (n = 515)
Web of Science (n = 166)
Embase (n = 67)
References from other sources (n = 0)
Citation searching (n = 0)
Grey literature (n = 0)
References removed (n = 167)
Duplicates identified manually (n = 0)
Duplicates identified by Covidence (n = 167)
Marked as ineligible by automation tools (n = 0)
Other reasons (n = 0)
Screening
Studies screened (n = 581)
Studies excluded (n = 492)
Studies sought for retrieval (n = 89)
Studies not retrieved (n = 0)
Studies assessed for eligibility (n = 89)
Studies excluded (n = 78)
Abstract only (n = 15)
Study setting (n = 4)
Study design (n = 26)
Study population (n = 30)
Study outcomes (n = 2)
Wrong language (n = 1)
Included
Studies included in review (n = 11)
Included studies ongoing (n = 0)
Studies awaiting classification (n = 0)

Fig. 1 PRISMA flow diagram detailing the identification, screening, eligibility, and inclusion of studies in the systematic review

Lung microbiome community composition

Ten studies provided detailed information on bacterial community composition, which is presented in Table 3 [23, 24, 26–33]. Of 11 studies, 2 studies performed a PCA [24, 27] and 6 studies a PCoA [25, 28, 30–33] to visually assess the community composition. In these analyses, 5 out of 8 studies exhibited a difference in the community composition in ARDS compared to that of controls [24, 27, 28, 31, 32]. Findings of studies rated as poor quality are summarised in Table 3 only [23, 26, 29, 31, 33].

Mixed-type ARDS. In the study of Dickson et al. 2020, mechanically ventilated patients with mtARDS and nonARDS shared dominance of the phylum Verrucomicrobiota [24], as well as high levels of *Pasteurellaceae* (Pseudomonadota), *Moraxellaceae* (Pseudomonadota), *Streptococcaceae* (Bacillota), *Lactobacillaceae* (Bacillota), *Flavobacteriaceae* (Bacteroidetes), and *Veillonellaceae* (Bacillota). However, a notable contrast between the groups was the higher abundance of *Enterobacteriaceae* (Pseudomonadota) in mtARDS, being the second most

Table 1 Study characteristics

Study	Setting	Design	Patients, n	Controls, n	Age (years), mean	Male (%)	Inclusion criteria	Time of inclusion/sampling	ARDS type	Study quality
Dickson et al 2020	Academic Medical Center, Amsterdam	Cohort	17 ARDS (Total 91)	No controls	60.7 (Entire cohort)	55 (Entire cohort)	Patients admitted to the ICU in mechanical ventilation. Patients meeting ≥ two SIRS criteria and received no antibiotics prior to ICU admission	Within 24 h of ICU admission	mtARDS	Good
Hernández-Terán et al 2023	Instituto Nacional de Enfermedades Respiratorias, Mexico City	Cohort	30 ARDS	No controls	45.5	63.3	Emergency room admitted patients with flu like symptoms, difficulty breathing or SAT < 90% and ARDS due to influenza A	Within 48 h of hospital admission	pARDS - Influenza	Good
Kyo et al 2019	Hiroshima University Hospital	Case–control	40 ARDS	7 (Trauma, VAP, consciousness disorder)	67	70	Intubated and ventilated adult ICU patients with ARDS	Within 24 h of ICU admission	mtARDS—Pneumonia, sepsis, aspiration, and other	Fair
Zhang et al 2022	Jiangmen Central Hospital	Case–control	156 ARDS	28 (Mild pulmonary infection)		67.9	Adult patients with sepsis-induced ARDS	Within 24 h from ARDS diagnosis	epARDS and pARDS	Fair
Poor quality studies										
Du et al 2022	China-Japan Friendship Hospital, Beijing, China	Cohort	29 ARDS (Total 67)	No controls	64.0 (Entire cohort)	74.6	Adult ICU patients with community-acquired pneumonia (time from onset to ICU admission ≤ 7 days (extended up to 14 days))	Within 48 h of ICU admission	pARDS - pneumonia	Poor

Table 1 (continued)

Study	Setting	Design	Patients, n	Controls, n	Age (years), mean	Male (%)	Inclusion criteria	Time of inclusion/sampling	ARDS type	Study quality
Li et al 2024	Department of Critical Care Medicine at the First Affiliated Hospital of Harbin Medical University in Heilongjiang Province, China	Cohort	48 ARDS	No controls	61.5	43.8	Patients diagnosed with sepsis and ARDS. Patients with sepsis due to pulmonal infection were excluded	Day 1 and 3 of ICU admission	epARDS–sepsis	Poor
Dickson et al 2016	Multicenter (3 ICUs) University of Michigan Medical Center, Emory University Hospitals, and University of Colorado Denver	Case–control	68 ARDS	26 (Healthy non-smokers—from other cohort)	47.4	67	ARDS diagnosis in ICU	8.7 (±6.2) days after meeting ARDS criteria	mtARDS—Pneumonia, aspiration, sepsis, and other	Poor
Ye et al 2023	Panyu Central Hospital	Case–control	19 ARDS	36 (Sepsis)	67	73.7	Adult patients with sepsis and ARDS	Not specified	mtARDS–sepsis with both pulmonary or extrapulmonary infection	Poor
Schmitt et al 2020	Heidelberg University Hospital	Case–control	14 ARDS	15 (Oesophageal resection)	59.0	92.9	Adult patients undergoing major abdominal surgery with following sepsis-induced ARDS	Day 0 (ARDS onset), day 5 and day 10	epARDS - Sepsis	Poor

ETA

Table 1 (continued)

Study	Setting	Design	Patients, n	Controls, n	Age (years), mean	Male (%)	Inclusion criteria	Time of inclusion/sampling	ARDS type	Study quality
Panzer et al 2018	Zuckerberg San Francisco General Hospital	Cohort	16 ARDS (Total 74)	No controls	Only reported in groups of smoking status	Only reported in groups of smoking status	Intubated, and ventilated adult ICU patients with severe blunt trauma	Time of admission and 48 h later	epARDS–Trauma	Good
Imbert et al 2024	Pau and Bordeaux hospitals	Cohort	29 ARDS (Total 53)	No controls	Influenza: 58 Bacteria: 66	Influenza: 56 Bacteria: 73	Patients admitted to ICU for community-acquired influenza-, COVID or bacterial related ARDS	Within 24 h of ICU admission	pARDS–Influenza, bacterial pneumonia, and COVID-19	Good

ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit, ETA: Endotracheal aspirate, epARDS: extrapulmonary ARDS, pARDS: pulmonary ARDS, mtARDS: mixed-type ARDS, nonARDS: patients without ARDS, SIRS: Systemic inflammatory response syndrome, BAL: Bronchoalveolar lavage, VAP: Ventilator-associated pneumonia

Table 2 Sequencing methods

	Design	Sample Type	Sequencing Platform	Sequencing Type	16S Region/Target	Bioinformatics Pipeline
Panzer et al. 2018	Cohort	ETA	Illumina MiSeq	16S rRNA	V4	QIIME
Dickson et al. 2020	Cohort	Mini-BAL	Illumina MiSeq	16S rRNA	V4	Not reported
Du et al. 2022	Cohort	BAL	Illumina MiSeq	16S rRNA	V3–V4	Not reported
Hernández-Terán et al. 2023	Cohort	BAL and ETA	Illumina MiSeq	16S rRNA	V3-V4	QIIME2, DADA2
Imbert et al. 2024	Cohort	ETA	Illumina MiSeq	16S rRNA, ITS2	V4, ITS2	DADA2
Na-Na Li et al. 2024	Cohort	BAL	Illumina	16S rRNA	Not reported	Not reported
Dickson et al. 2016	Case–control	BAL	Illumina MiSeq	16S rRNA	V4	Not reported
Kyo et al. 2019	Case–control	BAL	Ion Torrent PGM	16S rRNA	V5–V6	QIIME v1.8.0
Schmitt et al. 2020	Case–control	BAL	Illumina MiSeq	16S rRNA	V4	SILVA
Zhang et al. 2022	Case control	BAL	Illumina NextSeq CN500	mNGS	Not applicable	Bowtie2
Ye et al. 2023	Case–control	BAL	Illumina	mNGS	Not applicable	Not reported

BAL: Bronchoalveolar Lavage, mini-BAL: Mini- Bronchoalveolar Lavage, ETA: Endotracheal Aspirate, rRNA: Ribosomal RNA, ITS2: Internal Transcribed Spacer 2, mNGS: Metagenomic Next-Generation Sequencing, QIIME: Quantitative Insights Into Microbial Ecology, DADA2: Divisive Amplicon Denoising Algorithm 2, PGM: Personal Genome Machine

abundant family, while practically being absent in nonARDS [24].

Pulmonary ARDS. Zhang et al. reported a lower prevalence and reduced abundance of *Sphingomonas* (Pseudomonadota), *Curvibacter* (Pseudomonadota), *Brevundimonas* (Pseudomonadota), *Vibrio* (Pseudomonadota), *Hydrobacter* (Bacteroidetes), *Rhodococcus* (Actinomycetota), and *Microbacterium* (Actinomycetota) in pARDS compared to mechanically ventilated patients with nonARDS [27]. In contrast, *Shigella* (Pseudomonadota) and specifically *Escherichia coli* (Pseudomonadota), as well as *Staphylococcus* (Bacillota), were more prevalent in pARDS than in nonARDS, although their abundance was similar when present [27]. Notably, sampling was obtained before any antibiotic treatment, and after seven days of treatment in a subgroup of these patients (n = 30), the microbiome composition was largely unaffected [27]. Hernández-Terán et al. showed that among patients with pARDS caused by influenza virus [28], Bacillota was the most abundant phylum, followed by Bacteroidota, Pseudomonadota, and Actinomycetota. Within these phyla, the most abundant genera were *Prevotella* (Bacteroidota), *Streptococcus* (Bacillota), and *Veillonella* (Bacillota). Other genera, such as *Erwinia* (Pseudomonadota), *Haemophilus* (Pseudomonadota), *Staphylococcus* (Bacillota), and *Oribacterium* (Bacillota), were found in many samples but in low abundance [28].

Table 3 Study results

Study	Taxonomy	Focus	Lung composition in ARDS	α-diversity	β-diversity	Clinical outcomes
Dickson et al., 2020	Family	Associations between the lung microbiome and clinical outcomes in critically ill patients	In ARDS: Higher abundances of *Enterobacteriaceae*	No statistically significant difference (Shannon index: p = 0.13, community richness: p = 0.83)	β-diversity differed significantly between ARDS and nonARDS, p = 0.013	High abundance of *Lachnospiraceae* and *Enterobacteriaceae* predicted fewer ventilator-free days in both mtARDS and nonARDS patients. Elevated lung bacterial DNA burden predicted poor ICU outcomes
Hernández-Terán et al., 2023	Genus	Composition in influenza-induced ARDS. Deceased versus recovered	Most dominant genera in deceased patients: *Staphylococcus* and *Granulicatella* Most dominant genera in recovered: *Veillonella, Streptococcus and Rothia*	Lower α-diversity in patients receiving prior antibiotics (Chao1 Index, p = 0.01), lower α-diversity among diseased than recovered (Shannon index, p = 0.0004)	β-diversity differed significantly between deceased and recovered patients, p = 0.009	In pARDS, *Staphylococcus* and *Granulicatella* dominated in non-survivors; *Streptococcus* and *Rothia* in survivors
Kyo et al., 2019	Genus	Lung microbiome association to inflammation and mortality	No differences in community structure between ARDS and controls	Lower α-diversity in ARDS (Shannon Index, p = 0.03) than controls	No differences in β-diversity were observed between ARDS survivors, non-survivors, and nonARDS controls (no p-value reported)	In mtARDS reduced relative abundance of Betaproteobacteria was associated with higher mortality (HR 0.953, p = 0.0056)
Zhang et al., 2022	Species	Composition in epARDS versus pARDS	In epARDS: Higher positive rate for *Escheria coli* than pARDS and controls In pARDS: Higher positive rate for *Escheria coli, Staphylococcus Haemolyticus* and *Fungi* than controls	Lower α-diversity in pARDS than epARDS (based on positivity and abundance)	β-diversity differed between pARDS, and controls (R = 0.019, p = 0.001), and between epARDS and controls (R = 0.033, p = 0.004), but not between pARDS and epARDS, R = 0.007, p = 0.285	In epARDS, *Staphylococcus haemolyticus* and *Escherichia coli* were present in both groups but more prevalent in non-survivors. *Bilophila* presence in pARDS and epARDS was associated with higher mortality
Poor quality studies:						
Du et al., 2022	Family	Clinical factors associated with lung microbiome in severe CAP patients	Most abundant taxa: *Pseudomonadaceae, Moraxellaceae, Streptococcaceae, Staphylococcaceae, Prevotellaceae, and Actinomycetaceae*	No statistically significant difference (Shannon index: p = 0.95, Community richness: p = 0.35)	No significant differences in β-diversity between ARDS and nonARDS	Relative abundance of *Prevotellaceae* and *Actinomycetaceae* predicted clinical improvements ICU length of stay: ARDS 12 days vs. nonARDS 7.5 days (p = 0.03); ICU mortality: 25.6% vs. 0%
Li et al., 2024	Species	The importance of throat and intestinal microbiome in lung composition in septic ARDS	Increase in abundance *of Acinetobacter, Enterococcus* and *Pseudomonas* on the third day compared to the first day, and a reduction in *Enterobacteriaceae, Escherichia-Shigella* and *Coryneaceae*	α-diversity was lower at day three compared to day one (Chao1 index, no p-value)	β-diversity shifts observed between day 1 and day 3 in ARDS (no p-value reported)	ICU stay: ARDS = 12 days vs. nonARDS = 7.5 days (p = 0.03); ICU mortality: ARDS 25.6% vs. nonARDS 0%
Dickson et al., 2016	Genus	Lung microbiome composition under critical illness	*Neisseria* and multiple Bacteroidota species (*B. fragilis*, *B. thetaiotaomicron*, *B. faecichinchillae*, and *B. salyersiae)* were more prevalent and abundant in mtARDS patients than healthy controls		β-diversity differed significantly between ARDS and healthy controls, p ≤ 0.001	

Table 3 (continued)

Study	Taxonomy	Focus	Lung composition in ARDS	α-diversity	β-diversity	Clinical outcomes
Ye et al., 2023	Species	Lung microbiome and sepsis-induced ARDS	In ARDS: Higher relative abundances of *Pseudomonas aeruginosa, Klebsiella pneumonia, Cytomegalovirus, Streptococcus pneumonia, Candida Albicans,* and *E. coli*			
Schmitt et al., 2020	Genus	Lung microbiome changes in sepsis-induced ARDS following surgery	In epARDS: Lower abundances of *Prevotella, Veillonella, Haemophilus, Campylobacter*	Lower α-diversity in epARDS (Shannon Index, p = 0.007) than controls	β-diversity differed significantly between sepsis-induced ARDS and healthy controls, R = 0.07, p = 0.002	In epARDS high α-diversity correlated negatively with both ventilator-free days and length of ICU stay
ETA:						
Panzer et al., 2018	Genus	Lung microbiome association to smoking status and ARDS development in severe, blunt trauma patients	Relative enrichment of: *Enterobacteriaceae, Prevotella*, and *Fusobacterium*	Increased α-diversity after 48 h compared to 0 h	β-diversity increased between 0 and 48 h	
Imbert et al., 2024	Genus	Lung microbiome composition differences in Influenza-, COVID-19-, and bacterial CAP-related ARDS	Higher abundances of *Acinetobacter* and *Actinomyces* in bacterial related ARDS compared to Influenza, and higher abundances of *Prevotella* and *Pyramidobacter* compared to COVID-19	Lower α-diversity in bacterial related ARDS than COVID-19 (Shannon index, p = 0.04)	β-diversity differed significantly between influenza-, COVID-19-, and bacterial CAP-related ARDS patients (p = 0.05)	Mortality in ARDS: Influenza 40%, COVID-19 35%, bacterial 33%; not analysed in relation to microbiome

ARDS: Acute respiratory distress syndrome, epARDS: extrapulmonary ARDS, pARDS: pulmonary ARDS, mtARDS; mixed-type ARDS, nonARDS: patients without ARDS, CAP: community-acquired pneumonia

Extrapulmonary ARDS. As reported by Zhang et al. [27], epARDS exhibited a higher prevalence and abundance of *Comamonas* (Pseudomonadota) compared to nonARDS, whereas *Hydrobacter* (Bacteroidota) had a lower prevalence but a similar abundance. Of note, *Porphyromonas* (Bacteroidetes) was highly abundant in both epARDS and nonARDS, with no between-group differences in prevalence or abundance. When comparing epARDS to pARDS, the main contrast was a higher prevalence and abundance of *Cutibacterium* (Actinomycetota) in the former [27].

ETA-based studies. In trauma patients who developed epARDS in the first eight days, Panzer et al. showed an enrichment of *Enterobacteriaceae* (Pseudomonadota), *Prevotella* (Pseudomonadota), and *Fusobacterium* (Fusobacteriota) [32]. In pARDS patients, Imbert et al. [30], showed that bacterial CAP-related ARDS had higher abundances of *Acinetobacter* (Pseudomonadota) and *Actinomyces* (Actinomycetota) compared to Influenza-related ARDS, and higher abundances of *Prevotella* (Bacteroidota) and *Pyramidobacter* (Synergistota) compared to COVID-19-related ARDS [30].

Mixed-type ARDS. When comparing mtARDS to nonARDS, Kyo et al. found a lower Shannon diversity index in ARDS patients [25]. Dickson et al. 2020 found no difference in the Shannon diversity index or community richness between groups of mtARDS and nonARDS, as within-group variation was much greater than differences between groups [24].

Pulmonary ARDS. Regarding pARDS, α-diversity was reported to be lower than in both epARDS and nonARDS by Zhang et al., but comparable between the latter two groups [27]. Notably, in a subgroup of pARDS patients, bronchoalveolar lavage fluid (BALF) was obtained before any antibiotic treatment and repeated after seven days of supportive intensive care, including broad-spectrum antibiotics. No marked change in α-diversity was found between time points [27]. In contrast, Hernández-Terán et al., which lacked a comparator group, reported lower α-diversity in patients who had received antibiotics before hospitalisation [28].

ETA-based studies. Imbert et al. showed a lower α-diversity in bacterial CAP-related ARDS compared to COVID-19-related ARDS [30].

Lung microbiome diversity

A total of eight studies commented on α-diversity (see Fig. 2) [24, 25, 27–32]. Results of poor-quality studies are presented in Table 3 [29, 31].

Patient-related outcomes

Six studies reported different patient-related outcomes [24, 25, 27–29, 31].

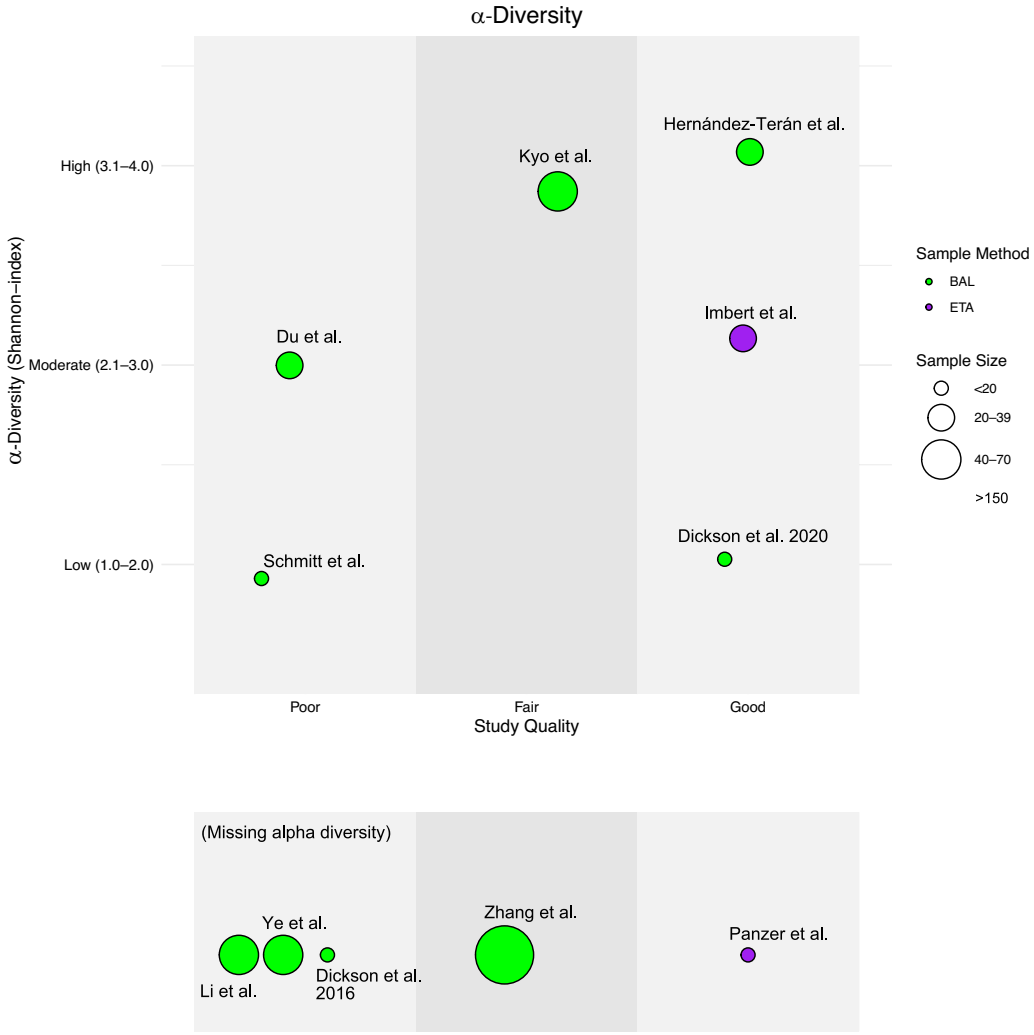

Fig. 2 Bubble plot showing α-diversity, study quality, and sample method across studies. Circle size indicates sample size

Kyo et al. reported that a reduced relative abundance of *Betaproteobacteria* (Pseudomonadota) was associated with higher mortality in mtARDS [25]. In pARDS, Zhang et al. demonstrated the presence of *Staphylococcus haemolyticus* (Bacillota) and *Escherichia coli* (Pseudomonadota) in both survivors and non-survivors, whereas they were more prevalent among non-survivors in epARDS [27]. Furthermore, they showed across both pARDS and epARDS, that specific presence of *Bilophila* (Thermodesulfobacteriota, previously Pseudomonadota) was associated with an elevated mortality risk, whereas α-diversity did not differ between survivors and non-survivors in either pARDS or epARDS [27]. Hernández-Terán et al. found that in pARDS *Staphylococcus* and *Granulicatella* spp. (both Bacillota) were dominant among non-survivors, whereas *Streptococcus* (Bacillota) and *Rothia* (Actinomycetota) were dominant among survivors [28]. In this study, α-diversity was furthermore lower in non-survivors compared to survivors.

Dickson et al. 2020 reported a high abundance of *Lachnospiraceae* (Bacillota) and *Enterobacteriaceae* (Pseudomonadota) to be the strongest predictors of fewer ventilator-free days in both mtARDS and nonARDS patients [24]. Additionally, a high lung bacterial DNA burden was identified as an independent predictor of poor ICU outcome. A tenfold increase in bacterial DNA corresponded to a hazard ratio of 0.43 for liberation from mechanical ventilation [24]. In contrast, α-diversity did not predict ventilator-free days.

For further details, including results of poor-quality studies, see Table 3 [29, 31].

Discussion

The available studies on lung microbiome composition, abundance, and diversity, and their impact on clinical outcomes in patients with ARDS, as compiled in the present systematic review, are heterogeneous. They vary greatly in terms of design, patient populations, and

quality. Together, they do, nevertheless, indicate that the lung microbiome composition in both pARDS and epARDS differs from that of healthy individuals.

Based on the included studies, it is difficult to identify a specific shift in pulmonary microbiome composition due to the heterogeneity of the studies. Major differences exist in the type of ARDS studied—such as mtARDS, pARDS, and epARDS—as well as in aetiology, whether viral, bacterial, or non-infectious. Additionally, comparator groups vary markedly across studies, ranging from healthy volunteers to critically ill, mechanically ventilated patients without ARDS.

However, a general pattern does seem to be present across studies. The healthy pulmonary microbiome primarily consists of bacteria also found in the oropharyngeal microbiome [34], but with specific enrichment of certain species in the lung. Pseudomonadota and Bacteroidota are the dominant phyla [9–12]. Hence, from the findings reviewed here, both mtARDS and pARDS appear to involve a shift in phylum dominance, with a relative decrease in Pseudomonadota and Bacteroidota, particularly in favour of Bacillota [27, 28].

From the reviewed studies, it is unclear whether this shift is consistently associated with a change in the diversity of the microbiome. While key genera such as *Prevotella* and *Porphyromonas*, which are highly abundant in the healthy lung, remain present, their relative abundance appears to be reduced, with an emergence of *Streptococcaceae* and *Veillonella*, and to a lesser extent, *Staphylococcaceae*. Meanwhile, an increased abundance of genera such as *Shigella*, *Enterobacteriaceae* (notably *Escherichia coli*), *Neisseria*, and various anaerobic *Bacteroides* species—normally present at low abundance or absent from the pulmonary microbiome—is observed [24, 27, 32]. Taxonomic and molecular analyses suggest that these are derived from the lower intestinal tract, including *Enterobacteriaceae*, thus indicating that enrichment of bacterial genera derived from the gastrointestinal microbiome is at play.

In epARDS, when compared to individuals without critical illness, there is a lower abundance of genera across all phyla, indicating a reduction in the normal lung microbiome. This decline particularly affects anaerobic bacteria, such as Prevotella spp., and is typically driven by the dominance of a single other species, which varies between patients. Panzer et al. reported the dominance of a single species, with *Enterobacteriaceae* being the predominant group. However, their findings are based solely on ETAs from only 16 patients and should be interpreted with caution.

Clinical implications

While findings on the prognostic impact of microbiome diversity remain uncertain—given that no consistent changes in diversity were observed across the included studies—the aforementioned shifts in microbiome composition do appear to have prognostic implications. Suppression of genera within Pseudomonadota, that are normally present within the healthy lung, as well as the presence of specific gut-derived bacteria such as *Escherichia coli, Bilophila*, and *Staphylococcus*, have been linked to a higher mortality risk in several of the studies [25, 27, 28]. Furthermore, a preserved high relative abundance of *Prevotellaceae* and *Actinomycetaceae,* which are also part of the normal healthy pulmonary microbiome, seemed to be associated with increased ventilator-free days and improved clinical recovery.

The present findings are consistent with the concept of dysbiosis as a mechanism contributing to the development and progression of ARDS. A process that is triggered by pulmonary inflammation and the invasion of pathogenic microbes that further drives this in a vicious cycle. Gut-derived bacteria appear to play a critical role, supporting the hypothesis that the translocation of gut bacteria to the lung also contributes to the pathogenesis of lung injury. The concept of the lung-gut axis, which refers to the pathophysiological interplay between the lung and gut in disease processes, has been widely discussed in sepsis and ARDS [35, 36]. In sepsis, the disruption of the intestinal barrier function allows intact microbes, particularly from the lower gastrointestinal tract, to translocate and has been proposed as a mechanism for their entry into the lung [37, 38]. However, there is currently no direct evidence that gut-derived bacteria in the lung are not simply present due to microaspiration caused by endotracheal intubation [5]. This complex interplay underscores the importance of comparing gut and lung microbial dynamics. While the gut microbiome is characterised by high microbial density and diversity and shows relatively consistent dysbiosis patterns across conditions, the lung microbiome presents a different picture. It is a low-biomass environment, more prone to contamination, and shaped by unique influences like microaspiration, mechanical ventilation, and distinct local innate and adaptive immune responses [39].

These complexities highlight the challenge of interpreting lung microbiome alterations in ARDS. Most studies collected only a single respiratory sample after diagnosis, which limits the ability to capture temporal changes and hinders efforts to distinguish whether observed dysbiosis is a cause or consequence of the condition. Supporting this, a study examined ETA samples from ICU patients with severe blunt trauma and found, as expected, a notable divergence in bacterial composition at 48 h after admission [32]. Interestingly, ARDS development was not associated with baseline composition, but rather with lung bacterial composition at 48 h, particularly showing an enrichment of the gut-associated *Enterobacteriaceae*

family. This suggests that early shifts in bacterial composition may influence disease progression in ARDS [32].

Limitations

It is important to acknowledge several limitations in the included studies and the conclusions that can be drawn from this systematic review. Firstly, quality assessments were conducted for the included studies, and a considerable proportion of the studies were classified as poor quality based on our assessments (see Additional file 2). However, it is worth noting that there is currently no validated or universally accepted tool for evaluating the quality of microbiome studies. Existing tools, such as the Newcastle–Ottawa Scale, were developed for broader epidemiological research and may not fully capture the methodological nuances specific to microbiome investigations.

As previously mentioned, the studies further compared highly heterogeneous populations, including mtARDS, pARDS, and epARDS of various aetiologies.

Additionally, the impact of different treatments, including supportive therapies as mechanical ventilation and antibiotic treatments, on microbiome composition, diversity, and pulmonary inflammatory response were not consistently controlled across studies. Antibiotic exposure is a major confounder in microbiome studies of critically ill patients. While Hernández-Terán et al. observed reduced microbial diversity and increased *Actinobacteria* in patients pre-treated with antibiotics, another found no clear associations [24, 29], reflecting the methodological variability and complexity of isolating antibiotic effects from the broader pathophysiology of ARDS [24, 29]. Although not included in our review due to the lack of ARDS-specific analyses, a study of 301 mechanically ventilated patients (including 72 with ARDS) identified a low-diversity cluster associated with prior antibiotic use and increased ARDS incidence [40]. Together, these findings highlight the need to account for antibiotic exposure when interpreting lung microbiome alterations.

Additional clinical outcomes were not consistently reported across studies and often not analysed in relation to the lung microbiome, which limited the ability to assess whether microbiota alterations were associated with broader clinical outcomes.

The pulmonary microbiome differs subtly between individuals, in part because of variations in microbiome composition and diversity [24]. Furthermore, the microbiome is unlikely to be static, even in a healthy state, as it continuously adapts to environmental and physiological changes [41], and it may thus vary substantially within an individual, i.e., both temporally and spatially between different lung compartments. In this context, two of the included studies[30, 32] relied solely on ETA, raising concerns about upper airway and saliva contamination and representativeness. However, research on the spatial distribution of bacteria in healthy individuals show that BAL samples closely resemble that of the oropharynx, with minimal site-specific microbial enrichment or bronchoscope contamination [5]. Though, it remains unclear whether this similarity reflects true microbial overlap or subtle upper airway contamination of BAL samples as well.

Another common limitation includes variations in laboratory and bioinformatics methods (see Table 2). This is particularly important in lung microbiome research, where microbial biomass is low, and contamination risks are high. 16S rRNA sequencing, frequently used, is sensitive to primer selection and lacks species-level resolution, which may obscure clinically relevant microbial shifts in ARDS. Whole-genome shotgun sequencing offers deeper insights but is limited by host DNA contamination, often exceeding 90% of reads [42, 43]. Also, more recently, Nanopore has emerged as an alternative to Illumina-based platforms, enabling full-length 16S sequencing and real-time analysis. However, Nanopore has lower accuracy and less developed analysis tools. Illumina sequencing, on the other hand, provides highly accurate short reads with well-established pipelines, though limited read lengths restrict species-level identification [44].

These methodological differences may contribute to inconsistencies in findings across studies. Another key factor contributing to conflicting outcomes is the presence of random error, primarily due to small sample sizes in multiple studies and the associated risk of type II error [45]. Many of the prognostic studies relied on comparisons between survivors and non-survivors, but to draw definitive conclusions, prospective studies are necessary.

Another limitation of this review is the large discrepancy between the number of records initially identified in PubMed and the final number of included studies. While this may suggest potential for refinement in the search strategy, the discrepancy is primarily due to the exclusion of non-original research (e.g., reviews, editorials) and studies that focused on respiratory diseases where ARDS was not strictly defined.

Conclusion

While methodological heterogeneity and varying study quality warrant cautious interpretation, this systematic review highlights a state of dysbiosis in the pulmonary microbiome across ARDS of various aetiologies. Hence, the dominant phyla are displaced while enrichment occurs with bacteria primarily derived from the lower gastrointestinal tract. These shifts may be related to disease severity, as suggested by potential associations with fewer ventilator-free days, and mortality. To advance our understanding, future studies must adopt standardised

methods, including strict definitions, inclusion criteria, uniform sampling and microbiome analysis techniques and consideration of a larger, well-characterised patient population. Additionally, integrating analyses of the spatial organisation of the lung microbiome, along with studies capable of collecting samples before and after ARDS onset, could provide critical insights into its structural dynamics and potential role in disease progression. The development of consensus recommendations for study design, sampling and analysis would be an important step to guide future research efforts to address this challenging condition.

Abbreviations

ARDS	Acute respiratory distress syndrome
PRISMA	Preferred reporting items for systematic reviews
ICU	Intensive care unit
ETA	Endotracheal aspirates
BAL	Bronchoalveolar lavage
PCA	Principal components analysis
PCoA	Principal coordinates analysis
NOS	Newcastle–Ottawa Scale
AHRQ	Agency for Healthcare Research and Quality
mtARDS	Mixed-type ARDS
pARDS	Pulmonary ARDS
epARDS	Extrapulmonary ARDS
nonARDS	Patients without ARDS
CAP	Community-acquired pneumonia
BALF	Bronchoalveolar lavage fluid

Supplementary Information

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Additional file 1.

Additional file 2.

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Author contributions

KS conceived the study, collected and interpreted the data, prepared the first draft, table, and figure, and contributed to revisions. JUU contributed to data collection, interpretation, and manuscript revisions. ANW, AB, UWI, and AR were involved in data interpretation and provided critical revisions. RRP contributed to data interpretation, revisions, and supervision. RMGB co-authored the first draft, contributed to data interpretation and revisions, and provided supervision throughout the project.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interest

The authors declare no competing interests.

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